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TITLE: Direct Test for Neuroinflammation with [11C]DAP-713-PET Scanning

PRINCIPAL INVESTIGATOR: Martin Pomper

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Baltimore, MD 21205

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Fort Detrick, Maryland 21702-5012

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Pomper, Martin; Haley, Robert; Coughlin, Jennifer; Wang, Yuchuan

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
This project concerns the non-invasive detection of inflammation in the brains of individuals suffering from the Gulf War Illness (GWI). We are using quantitative positron emission tomography (PET) using [11C]DPA-713 (DPA). DPA binds to the translocator protein (TSPO), which is located on the outer mitochondrial membrane and is an established biomarker of neuroinflammation. The study intends to enroll 10 patients and 10 appropriately matched healthy control subjects. The study is a collaboration between Johns Hopkins University and the University of Texas Southwestern Medical Center, where a carefully vetted population of individuals with GWI exists. PET imaging will be undertaken at Johns Hopkins.

15. SUBJECT TERMS
molecular imaging; PET; Gulf War Illness; DPA-713; distribution volume; neuroinflammation

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INTRODUCTION:

This project concerns the non-invasive detection of inflammation in the brains of individuals suffering from the Gulf War Illness (GWI). We are using quantitative positron emission tomography (PET) using [^{11}C]DPA-713 (DPA). DPA binds to the translocator protein (TSPO), which is located on the outer mitochondrial membrane and is an established biomarker of neuroinflammation. The study intends to enroll 10 patients and 10 appropriately matched healthy control subjects. The study is a collaboration between Johns Hopkins University and the University of Texas Southwestern Medical Center, where a carefully vetted population of individuals with GWI exists. PET imaging will be undertaken at Johns Hopkins.

KEYWORDS:

molecular imaging; PET; Gulf War Illness; DPA-713; distribution volume; neuroinflammation

ACCOMPLISHMENTS:

What were the major goals of the project?

- To identify, contact, and screen subjects for study.
- To perform [^{11}C]DPA-713 PET to study neuroinflammation in GWI and controls.
- Continued vetting, calling and screening of candidates.
- Recruitment and scanning of three patients.
- Analysis of patient studies (on a rolling basis).
- Refinement of image analysis for [^{11}C]DPA-713 PET.

What was accomplished under these goals?

We have continued to recruit and scan eligible subjects and matched controls through our collaboration with the UTSW group. This is ongoing. We continue to analyze the data, on a rolling basis, for these individuals. We have also refined our analysis of the PET imaging studies in several ways: (1) We developed a more sensitive and accurate method for metabolite correction, which is critical to the analysis; (2) We are working on ways of generating quantitative data while avoiding placement of an arterial catheter. The current need for arterial catheter placement is a mild but not insignificant difficulty for recruitment; and, (3) we have submitted a manuscript acknowledging this grant and project related to plasma sampling of patients and the relationship of inflammatory markers to expression of TSPO, the target for our PET agent, [^{11}C]DPA-713.

What opportunities for training and professional development has the project provided?

In order to undertake this project we have retained one and hired an additional research study coordinator. We have also hired an analytical chemist to upgrade our metabolite studies. Funds for those individuals were obtained in part from outside of the grant as they are not 100% dedicated to the project. All of this required training. We have also entered several new collaborations, including one abroad, to understand better the meaning of TSPO signal.

How were the results disseminated to communities of interest?

We have not yet published the primary paper that will derive from this work. As our sample size is too small it is not useful to publish interim analyses. This is standard procedure for us. We have performed [^{11}C]DPA-713 imaging in a variety of patient populations, most recently in active and recently former NFL players (published several months ago in *JAMA Neurology*). These publications come once the data are in and analyzed. However, interim data are presented at national and international meetings. The PI often discusses TSPO imaging at these meetings and notes the patient populations, including Gulf War Veterans, that are studied.

What do you plan to do during the next reporting period to accomplish the goals?

We will continue robust recruitment and analysis.

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

This is the first project to study neuroinflammation in this patient cohort.

What was the impact on other disciplines?

Better analysis of TSPO imaging has arisen. This is spreading to other work, such as TSPO imaging in schizophrenia and other populations.

What was the impact on technology transfer?

Nothing to report at this time.

What was the impact on society beyond science and technology?

Nothing to report at this time.

CHANGES/PROBLEMS:

Nothing to report

PRODUCTS:

Nothing to report – These items will be reported once finished with the project and publications are submitted.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Martin Pomper*
Project Role:	*Professor*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Planning, strategy, manuscript review*
Funding Support:	*NIH*

Name:	*Jennifer Coughlin*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	*Shepherding of patients through the trial, managing the study coordinators and data analysis.*
Funding Support:	*NIH/DoD*

Name:	*Yuchuan Wang*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Wang has left JHU to assume a position at Merck. He has trained and been replaced by his former colleague Dr. Yong Du, who continues the analysis.*
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

- Martin Pomper

Ended

Title: PSMA-associated PET imaging of CAR T cells

Time Commitments: 0.12 calendar months
Supporting Agency: Juno Therapeutics
Grants Contact: Jake Handy
PI: Pomper
Performance Period: 11/01/2015 – 10/31/2016
Level of Funding: $95,492
Description of Goals: To develop a PSMA-based molecular-genetic imaging system for tracking T cells.
Aim 1: Functional assessment of CAR T cells expressing PSMA (full length and truncated versions)
Aim 2: Evaluation of 18F-DCFPyL labelling and tracking of PSMA+ CAR T cells

Title: PSMA Directed Imaging of Prostate Cancer Focus on Androgen Receptor Dynamics
Time Commitments: 2.4
Supporting Agency: NIH/NCI U01CA183031
Grants Contacts: Yantian Zhang; Program Official; 240-276-5980; Yantian.zhang@nih.gov
PIs: Pomper/Deweese
Performance Period: 11/01/2014-10/31/2016
Level of Funding: $496,642
Description of Goals: The overall goal is to validate at least two positron-emitting, PSMA-targeted imaging agents clinically so that they can be used to full advantage in supporting existing and emerging therapies for a spectrum of patients suffering from PCa.
Aim 1. To image treatment-naïve patients with localized-locally advanced primary PCa using DCFBC-PET/magnetic resonance imaging, and correlate signal with that on MR concurrently obtained, as well as with tumor grade, PSMA expression and androgen receptor (AR) signaling before and after two months of neoadjuvant androgen deprivation (ADT).
Aim 2. To image patients with CRPC using DCFBC-PET/MR and correlate findings with bone and soft tissue biopsy.
Aim 3. To image patients with CRPC with DCFBC-PET/MR and correlate with standard 99mTc-based bone scan to guide stereotactic body radiation treatment (SBRT) in patients with oligometastatic disease.
Aim 4. Imaging CRPC with the second-generation, PSMA-targeted PET agent, [18F]DCFPyL.

New

Title: Study to Assess Single and Multiple Intravenous Doses of LY3002813 in Patients
Time Commitments: 0.12 calendar months
Supporting Agency: Shin Nippon Biomedical Laboratories
Grants Contacts: Christopher Hickey, Vice President Business Development, (443) 685-5800, chickey@snbl-cpc.com
PIs: Pomper
Performance Period: 04/08/16 - 04/07/17
Level of Funding: $ 925,149
Description of Goals: To perform human brain PET imaging as a biomarker to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple intravenous doses

of LY3002813 in patients with mild cognitive impairment due to Alzheimer's disease or mild to moderate Alzheimer's disease

Title: Systemic Radionuclide Therapy Targeted to VEGF Receptors in Tumor Vasculature
Time Commitments: 0.24 calendar months
Supporting Agency: HHSN261201500073C Backer-SIB Tech/ Pomper-JHU)
Grants Contacts: TBN
PIs: Pomper
Performance Period: 09/01/2015 - 05/31/2018
Level of Funding: $61,728.00
Description of Goals: To develop a radiotherapeutic agent that targets VEGF receptors to treat cancer

Title: Plasmid Selection and Characterisation
Time Commitments: 1.20 calendar months
Supporting Agency: Cancer Targeting Systems, Inc.
Grants Contacts: TBN
PIs: Pomper
Performance Period: 02/01/2016 - 07/31/2017
Level of Funding: $416,271.00
Description of Goals: To assess the functionality, yield and specificity of CpG-free and nanoplasmid variants of the CTS construct (backbone_PEG-3-HSV1-tk) to inform and hence enable selection of the optimal variant for further development, suitable for use on the clinic and to provide characterization data.

- Yong Du

New

Title: Dynamic Cardiac Imaging Using Dual-Head SPECT Camera
Time Commitments: 2.4 calendar months
Supporting Agency: AHA/ 16GRNT31090007
Grants Contacts: TBD
PIs: Du
Performance Period: 07/01/2016 - 06/30/2018
Level of Funding: $70,000
Description of Goals: The goal is to develop and validate dynamic cardiac imaging method using traditional dual-head SPECT system without using full SPECT acquisition

Title: Optimization and Validation of Improved Quantitative I-123 Brain SPECT Imaging
Time Commitments: 4.2 calendar months
Supporting Agency: NIH/ R01NS094227
Grants Contacts: TBD
PIs: Du
Performance Period: 07/01/2016 - 06/30/2020
Level of Funding: $200,000

Description of Goals: The goal is to develop, optimize, and validate methods that can provide accurate and reliable image measures of Parkinson's disease. These quantitatively accurate images can be used to monitor and improve the diagnosis and differentiation of the disease, which may lead to the development of new treatments

What other organizations were involved as partners?

Nothing to report